

compounds in spec

=> d his

(FILE 'HOME' ENTERED AT 13:41:40 ON 17 NOV 2004)

FILE 'REGISTRY' ENTERED AT 13:41:54 ON 17 NOV 2004

L1 STRUCTURE UPLOADED

L2 19 S L1

L3 946 S L1 FUL

L4 19 S L3

FILE 'CAPLUS' ENTERED AT 13:43:33 ON 17 NOV 2004

L5 88 S L3

FILE 'REGISTRY' ENTERED AT 13:46:39 ON 17 NOV 2004

L6 STRUCTURE UPLOADED

L7 34 S L6

L8 608 S L6 FUL

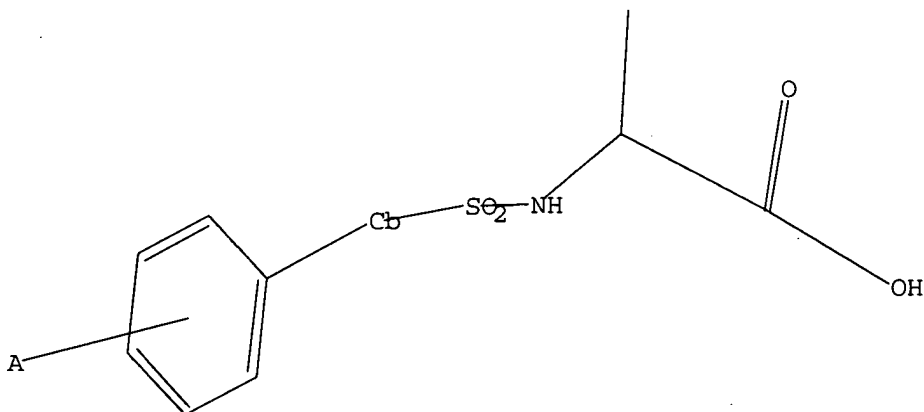
FILE 'CAPLUS' ENTERED AT 13:47:02 ON 17 NOV 2004

L9 57 S L8

=> d 16

L6 HAS NO ANSWERS

L6 STR



Structure attributes must be viewed using STN Express query preparation.

=> d bib abs 50-57

L9 ANSWER 50 OF 57 CAPLUS COPYRIGHT 2004 ACS on STN

AN 1998:742171 CAPLUS

DN 129:331047

TI Preparation and use of sulfonylaminocarboxylic acids as medicines

IN Thorwart, Werner; Schwab, Wilfried; Schudok, Manfred; Haase, Burkhard

PA Hoechst Aktiengesellschaft, Germany; Aventis Pharma Deutschland GmbH

SO Eur. Pat. Appl., 48 pp.

CODEN: EPXXDW

DT Patent

LA German

FAN.CNT 1

PATENT NO.

KIND

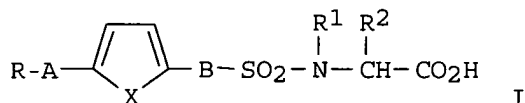
DATE

APPLICATION NO.

DATE

compounds in spec

PI	EP 877018	A1	19981111	EP 1998-108038	19980502
	EP 877018	B1	20030502		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	DE 19719621	A1	19981112	DE 1997-19719621	19970509
	AT 238984	E	20030515	AT 1998-108038	19980502
	PT 877018	T	20030930	PT 1998-108038	19980502
	ES 2195220	T3	20031201	ES 1998-108038	19980502
	CA 2237099	AA	19981109	CA 1998-2237099	19980507
	AU 9864823	A1	19981112	AU 1998-64823	19980508
	AU 732723	B2	20010426		
	JP 11060551	A2	19990302	JP 1998-162706	19980508
	BR 9801606	A	19990518	BR 1998-1606	19980508
	US 6451824	B1	20020917	US 1998-74693	19980508
	RU 2193027	C2	20021120	RU 1998-108979	19980508
	US 2003087945	A1	20030508	US 2002-170870	20020613
PRAI	DE 1997-19719621	A	19970509		
	US 1998-74693	A3	19980508		
OS	MARPAT 129:331047				
GI					



AB Title compds. [(I), R = (substituted)phenyl or heteroarom. group; R1 = H, (substituted)alkyl, 2-pyridinyl-methyl; R2 = H, (substituted)alkyl, (un)branched alkenyl, substituted phenyl; R1,R2 together = CO2H-substituted ring; A = bond, O, CY:CY; Y = H, bond; B = (CH2)1-6, O(CH2)1-5, CH:CH, bond; X = CH:CH, O, S], useful as matrix-metalloproteinase inhibitors, were prepared and tested. Thus, DL-homoserine lactone was reacted with PhO-4-C6H4-SO2Cl to give (±)-I [R = Ph; R1 = H; R2 = HOCH2CH2; A = O; B = bond; X = CH:CH(II)] in 73% yield. In in vitro fluorescence extinction tests with stromelysin and neutrophilic collagenase, II had IC50 of 4x10<sup>-7</sup> M and 1x10<sup>-8</sup>M resp.

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 51 OF 57 CAPLUS COPYRIGHT 2004 ACS on STN  
AN 1998:424117 CAPLUS  
DN 129:113523  
TI Use of matrix metalloproteinase inhibitors for treating neurological disorders and promoting wound healing  
IN Bocan, Thomas Michael Andrew; Boxer, Peter Alan; Peterson, Joseph Thomas, Jr.; Schrier, Denis; White, Andrew David  
PA Warner-Lambert Co., USA; Bocan, Thomas Michael Andrew; Boxer, Peter Alan; Peterson, Joseph Thomas, Jr.; Schrier, Denis; White, Andrew David  
SO PCT Int. Appl., 163 pp.  
CODEN: PIXXD2  
DT Patent  
LA English  
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9826773	A1	19980625	WO 1997-US21532	19971121
	W: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, HU, ID, IL, IS, JP,				

compounds in spec

KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

CA 2264692	AA	19980625	CA 1997-2264692	19971121
AU 9877353	A1	19980715	AU 1998-77353	19971121
AU 737117	B2	20010809		
EP 946166	A1	19991006	EP 1997-949584	19971121
EP 946166	B1	20040218		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

BR 9714142	A	20000229	BR 1997-14142	19971121
JP 2001507342	T2	20010605	JP 1998-527715	19971121
NZ 334925	A	20010629	NZ 1997-334925	19971121
EP 1366765	A1	20031203	EP 2003-18081	19971121

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, AL

AT 259640	E	20040315	AT 1997-949584	19971121
PT 946166	T	20040630	PT 1997-949584	19971121
ES 2212142	T3	20040716	ES 1997-949584	19971121
ZA 9711279	A	19980623	ZA 1997-11279	19971215
US 6340709	B1	20020122	US 1999-269123	19990319

PRAI US 1996-32753P P 19961217

EP 1997-949584 A3 19971121

WO 1997-US21532 W 19971121

OS MARPAT 129:113523

AB Matrix metalloproteinase inhibitors 4-RC6H4SO2NHCHR1COR2 [R = (un)substituted Ph; R1 = alkyl, phenylalkyl, phenyl; R2 = OH, alkoxy, NHOH] and 4-RC6H4C(:NR3)CR4R5CR6R7COR8 [R3 = (un)substituted OH, NH2; R4-R7 = H, F, (un)substituted alkyl; R8 = OH, SH] are useful for preventing and treating neurol. disorders, especially Alzheimer's, huntington's, and Parkinson's disease and amyotropic lateral sclerosis, and in promoting wound healing. IC50 for matrix metalloproteinase inhibition are reported for a number of compds. Formulations containing (R)-4-(4-NCC6H4)C6H4SO2NHCH(CO2H)CH2Ph, (S)-4-(4-H2NC6H4)C6H4SO2NHCH(CO2H)CH2C6H4OE t-3, and 4-(4-BrC6H4)C6H4SO2NHCH(CO2H)CHMe2 are reported.

RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 52 OF 57 CAPLUS COPYRIGHT 2004 ACS on STN

AN 1998:402296 CAPLUS

DN 129:76499

TI Method for treating and preventing heart failure and ventricular dilation

IN Peterson, Joseph T., Jr.

PA Warner-Lambert Co., USA

SO PCT Int. Appl., 178 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9825597	A2	19980618	WO 1997-US21934	19971202
	WO 9825597	A3	20001012		

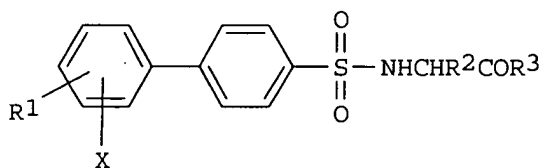
W: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, HU, ID, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR,

compounds in spec

GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA,  
GN, ML, MR, NE, SN, TD, TG

CA 2263886	AA	19980618	CA 1997-2263886	19971202	
AU 9855906	A1	19980703	AU 1998-55906	19971202	
AU 741768	B2	20011206			
BR 9714385	A	20000516	BR 1997-14385	19971202	
EP 1028716	A1	20000823	EP 1997-952246	19971202	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
NZ 334897	A	20010223	NZ 1997-334897	19971202	
JP 2001526631	T2	20011218	JP 1998-526758	19971202	
ZA 9711004	A	19981005	ZA 1997-11004	19971208	
US 5948780	A	19990907	US 1997-987167	19971208	
NO 9902769	A	19990809	NO 1999-2769	19990608	
KR 2000057444	A	20000915	KR 1999-705070	19990608	
PRAI US 1996-32631P	P	19961209			
WO 1997-US21934	W	19971202			
OS	MARPAT 129:76499				
AB	Matrix metalloproteinase inhibitors are useful for preventing and treating heart failure, and ventricular dilation in mammals. Thus, 2-(4'-bromobiphenyl-4-sulfonylamino)-3-methylbutyric acid was effective in protecting pigs in the pacing-induced heart failure model.				
L9	ANSWER 53 OF 57 CAPLUS COPYRIGHT 2004 ACS on STN				
AN	1998:352635 CAPLUS				
DN	129:32284				
TI	Biphenylsulfonamide matrix metalloproteinase inhibitors				
IN	O'Brien, Patrick Michael; Sliskovic, Drago Robert				
PA	Warner-Lambert Co., USA				
SO	U.S., 8 pp. CODEN: USXXAM				
DT	Patent				
LA	English				
FAN.CNT 1					
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI	US 5756545	A	19980526	US 1997-844598	19970421
PRAI	US 1997-844598		19970421		
OS	MARPAT 129:32284				
GI					



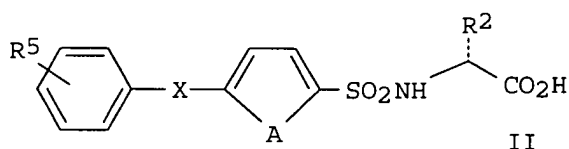
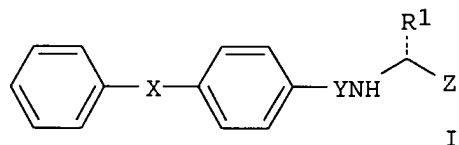
AB Compds. I (X = H, halo; R1 = alkyl, halo, nitro, amino, cyano, alkoxy, and alkoxy carbonyl; R2 = alkyl and substituted alkyl; and R3 = OH or NHOH) are useful for inhibiting matrix metalloproteinase enzymes in animals, and as such, prevent and treat diseases resulting from the breakdown of connective tissues. Sulfonation of 4-bromobiphenyl with chlorosulfonic acid, chlorination with POCl3, esterification with L-valine tert-Bu ester, and hydrolysis with trifluoroacetic acid gave (S)-2-(4'-Bromobiphenyl-4-sulfonylamino)-3-methylbutyric acid with 96% yield and m.p.

compounds in spec

192-193°.

RE.CNT 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 54 OF 57 CAPLUS COPYRIGHT 2004 ACS on STN  
AN 1998:66723 CAPLUS  
DN 128:188290  
TI Highly Selective and Orally Active Inhibitors of Type IV Collagenase  
(MMP-9 and MMP-2): N-Sulfonylamino Acid Derivatives  
AU Tamura, Yoshinori; Watanabe, Fumihiko; Nakatani, Takuji; Yasui, Ken; Fuji,  
Masahiro; Komurasaki, Tadafumi; Tsuzuki, Hiroshige; Maekawa, Ryuji;  
Yoshioka, Takayuki; Kawada, Kenji; Sugita, Kenji; Ohtani, Mitsuaki  
CS Shionogi Research Laboratories, Shionogi Co. Ltd., Osaka, 553, Japan  
SO Journal of Medicinal Chemistry (1998), 41(4), 640-649  
CODEN: JMCMAR; ISSN: 0022-2623  
PB American Chemical Society  
DT Journal  
LA English  
GI



AB Various N-sulfonylamino acid derivs., e.g. I (R1 = PhCH2, X = bond, Y = SO2, CO, Z = CONHOH, CO2H; R1 = indol-3-ylmethyl, X = bond, Y = SO2, Z = CONHOH, CO2H; R1 = Me2CH, X = O, Y = SO2, Z = CONHOH, CO2H) and II (R2 = indol-3-ylmethyl, R5 = H, OMe-4, OMe-3, A = CH:CH, X = bond; R2 = indol-3-ylmethyl, R5 = Me-4, A = S, X = bond; R2 = CHMe2, R5 = OMe-4, SMe-4, A = CH:CH, X = bond; R2 = CHMe2, R5 = OMe-4, A = S, X = bond; R2 = indol-3-ylmethyl, R5 = H, Me-4, CO2H-4, A = CH:CH, X = C.tplbond.C; R2 = indol-3-ylmethyl, R5 = NO2-2, NO2-4, Me-4, A = S, X = C.tplbond.C; R2 = CHMe2, R5 = Me-4, A = CH:CH, S, X = C.tplbond.C; R2 = CH2Ph, R5 = OMe-4, A = CH:CH, S, X = C.tplbond.C), were synthesized and evaluated for their in vitro and in vivo activities to inhibit type IV collagenase (MMP-9 and MMP-2). When the amino acid residue and the sulfonamide moiety were modified, their inhibitory activities were greatly affected by the structure of the sulfonamide moiety. A series of aryl sulfonamide derivs. containing biaryl, tetrazole, amide, and triple bond were found to be potent and highly selective inhibitors of MMP-9 and MMP-2. In addition, these compds. were orally active in animal models of tumor growth and metastasis. These results revealed the potential of the N-sulfonylamino acid derivs. as a new type of candidate drug for the treatment of cancer.

RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 55 OF 57 CAPLUS COPYRIGHT 2004 ACS on STN  
AN 1997:776147 CAPLUS  
DN 128:48054

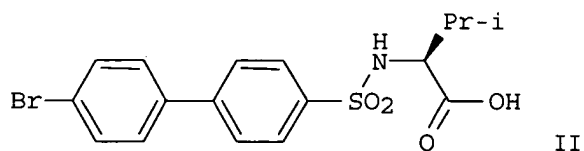
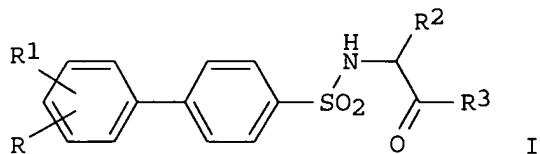
compounds in spec

TI Biphenylsulfonamide matrix metalloproteinase inhibitors  
 IN O'Brien, Patrick Michael; Sliskovic, Drago Robert  
 PA Warner-Lambert Company, USA  
 SO PCT Int. Appl., 29 pp.  
 CODEN: PIXXD2

DT Patent  
 LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9744315	A1	19971127	WO 1997-US6801	19970424
	W: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, GH, HU, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	CA 2253342	AA	19971127	CA 1997-2253342	19970424
	AU 9726803	A1	19971209	AU 1997-26803	19970424
	AU 713286	B2	19991125		
	EP 901466	A1	19990317	EP 1997-918788	19970424
	EP 901466	B1	20011031		
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	CN 1219166	A	19990609	CN 1997-194719	19970424
	CN 1077885	B	20020116		
	BR 9710841	A	19990817	BR 1997-10841	19970424
	NZ 332711	A	20000623	NZ 1997-332711	19970424
	JP 2000511175	T2	20000829	JP 1997-542377	19970424
	AT 207891	E	20011115	AT 1997-918788	19970424
	ES 2167733	T3	20020516	ES 1997-918788	19970424
	SK 282863	B6	20021203	SK 1998-1577	19970424
	EE 3965	B1	20030217	EE 1998-397	19970424
	PL 186416	B1	20040130	PL 1997-329929	19970424
	CZ 294063	B6	20040915	CZ 1998-3668	19970424
	ZA 9704223	A	19971210	ZA 1997-4223	19970515
	BG 63940	B1	20030731	BG 1998-102918	19981112
	NO 9805326	A	19990114	NO 1998-5326	19981116
	KR 2000011095	A	20000225	KR 1998-709253	19981116
	HK 1019585	A1	20020531	HK 1999-104791	19991027
PRAI	US 1996-17460P	P	19960517		
	WO 1997-US6801	W	19970424		
OS	MARPAT 128:48054				
GI					



compounds in spec

AB Title compds. I [R = H, halo; R1 = alkyl, halo, NO2, amino, aminoalkyl, cyano, alkoxy, alkoxy carbonyl, etc.; R2 = H, (un)substituted alkyl; and R3 = OH, alkoxy, or NHOH], are useful for inhibiting matrix metalloproteinase enzymes in animals, and as such, prevent and treat diseases resulting from the breakdown of connective tissues. For instance, 4-BrC6H4Ph underwent 4'-sulfonation (79%), conversion of the resultant sulfonic acid to the sulfonyl chloride (69%), sulfonamidation with H-Val-OtBu.HCl (60%), and deprotection of the ester (96%), to give title compound II. In an in vitro test for inhibition of the hydrolysis of thiopeptolide by collagenase or gelatinase B, II gave IC50 values of 3.24 and 8.34  $\mu$ M, resp.

L9 ANSWER 56 OF 57 CAPLUS COPYRIGHT 2004 ACS on STM

AN 1997:513624 CAPLUS

DN 127:162119

TI Preparation of N-sulfonylamino acid derivatives as metalloproteinase inhibitors

IN Watanabe, Fumihiko; Tsuzuki, Hiroshige; Ohtani, Mitsuaki

PA Shionogi and Co., Ltd., Japan

SO PCT Int. Appl., 128 pp.

CODEN: PIXXD2

DT Patent

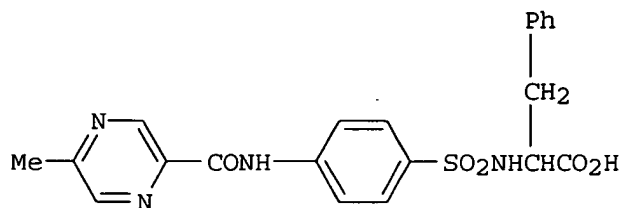
LA Japanese

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9727174	A1	19970731	WO 1997-JP126	19970122
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	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	CA 2242416	AA	19970731	CA 1997-2242416	19970122
	AU 9713195	A1	19970820	AU 1997-13195	19970122
	AU 715764	B2	20000210		
	CN 1214041	A	19990414	CN 1997-193226	19970122
	BR 9707010	A	19990720	BR 1997-7010	19970122
	EP 950656	A1	19991020	EP 1997-900747	19970122
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	NZ 325939	A	20000623	NZ 1997-325939	19970122
	JP 2001316254	A2	20011113	JP 2001-69135	19970122
	SK 282995	B6	20030109	SK 1998-984	19970122
	RU 2198656	C2	20030220	RU 1998-115659	19970122
	TW 575547	B	20040211	TW 1997-86100862	19970127
	NO 9803376	A	19980914	NO 1998-3376	19980722
	US 6150394	A	20001121	US 1998-120378	19980722
	US 6207698	B1	20010327	US 1998-120197	19980722
	US 6235768	B1	20010522	US 1999-307818	19990510
	AU 738793	B2	20010927	AU 2000-30222	20000501
	US 6441021	B1	20020827	US 2000-710904	20001114
	US 2003139379	A1	20030724	US 2002-188115	20020703
	US 2003225043	A1	20031204	US 2002-290245	20021108
PRAI	JP 1996-30082	A	19960123		
	JP 1996-213555	A	19960813		
	JP 1997-526728	A3	19970122		
	WO 1997-JP126	W	19970122		
	US 1998-120197	A3	19980722		

compounds in spec

US 1998-120383 A1 19980722  
US 2000-710094 B3 20001113  
OS MARPAT 127:162119  
GI



AB The title compds. R5R4R3SO2NR2CHR1COY [R1 = (un)substituted alkyl, aryl, aralkyl, heteroaryl, etc.; R2 = H, (un)substituted alkyl, etc.; R3 = single bond, (un)substituted arylene, etc.; R4 = single bond, CH:CH, C.tplbond.C, CO, CONH, N:N, NHCONH, NHCO, O, S, SO2NH, etc.; R5 = (un)substituted alkyl, cycloalkyl, etc.; Y = NHOH, OH; a proviso is given] are prepared The title compound (R)-I in vitro showed IC50 of 3.95  $\mu$ M against MMP-9 (gelatinase B).

L9 ANSWER 57 OF 57 CAPLUS COPYRIGHT 2004 ACS on STN

AN 1997:69816 CAPLUS

DN 126:89360

TI Preparation of [(isoxazolinyalcanoyl)amino]alkanoates and analogs as integrin antagonists

IN Voss, Matthew Ernst; Jadhav, Prabhakar Kondaji; Smallheer, Joanne Marie; Batt, Douglas Guy; Pitts, William John; Wityak, John

PA Du Pont Merck Pharmaceutical Company, USA

SO PCT Int. Appl., 331 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

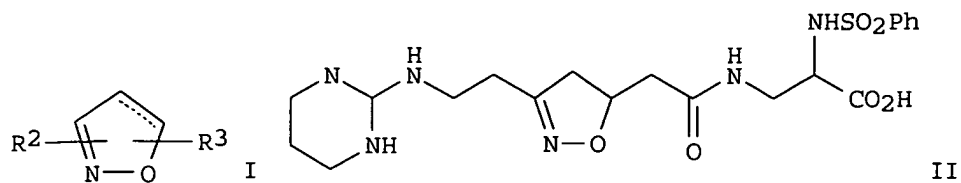
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9637492	A1	19961128	WO 1996-US7646	19960524
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	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 5710159	A	19980120	US 1996-647132	19960509
	CA 2221980	AA	19961128	CA 1996-2221980	19960524
	AU 9658762	A1	19961211	AU 1996-58762	19960524
	ZA 9604195	A	19971124	ZA 1996-4195	19960524
	EP 828737	A1	19980318	EP 1996-920476	19960524
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 11506436	T2	19990608	JP 1996-535899	19960524
PRAI	US 1995-450646	A	19950525		
	US 1995-455768	A	19950531		
	US 1996-647132	A	19960509		
	WO 1996-US7646	W	19960524		

OS MARPAT 126:89360

GI



compounds in spec



AB Title compds. [(addnl.-substituted) I; R2 = Z2Z1R1; R1 = N-containing heterocyclyl; R3 = Z3ZR; R = CO2H, alkoxy carbonyl, SO3H, CONHNHSO2CF3, etc.; Z = bond (un)substituted alkylene; Z1 = bond, (O- or N-interrupted)alkylene, CO, alkanoyl(alkyl), NHCO, etc.; Z2 = bond, alkylene, phenylene, etc.; Z3 = (alkylene)carbonylimino(alkyl), etc.; dashed line = optional bond] were prepared as integrin antagonists (no data). Thus, R4(CH2)3CH:NOH (R4 = phthalimido) (preparation given) was chlorinated and the product cyclocondensed with CH2:CHCH2CO2CMe3 to give, after deprotection, tert-Bu 3-(3-aminopropyl)-2-isoxazoline-5-acetate. The latter was N-alkylated with 2-methylthio-3,4,5,6-tetrahydropyrimidine hydroiodide to give, after saponification, amidation by H2NCH2CH(NHSO2Ph)CO2Me, and saponification, title compound II.

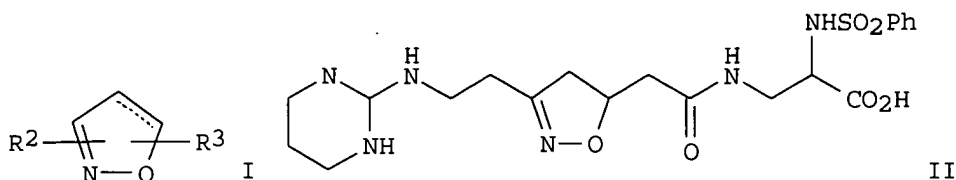
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compounds in spec

=> d bib abs hitstr 57

L9 ANSWER 57 OF 57 CAPLUS COPYRIGHT 2004 ACS on STN  
AN 1997:69816 CAPLUS  
DN 126:89360  
TI Preparation of [(isoxazolinyllalkanoyl)amino]alkanoates and analogs as  
integrin antagonists  
IN Voss, Matthew Ernst; Jadhav, Prabhakar Kondaji; Smallheer, Joanne Marie;  
Batt, Douglas Guy; Pitts, William John; Wityak, John  
PA Du Pont Merck Pharmaceutical Company, USA  
SO PCT Int. Appl., 331 pp.  
CODEN: PIXXD2  
DT Patent  
LA English  
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9637492	A1	19961128	WO 1996-US7646	19960524
	W: AM, AT, AU, AZ, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, HU, JP, KG, KR, KZ, LT, LU, LV, MD, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, TJ, TM, UA, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 5710159	A	19980120	US 1996-647132	19960509
	CA 2221980	AA	19961128	CA 1996-2221980	19960524
	AU 9658762	A1	19961211	AU 1996-58762	19960524
	ZA 9604195	A	19971124	ZA 1996-4195	19960524
	EP 828737	A1	19980318	EP 1996-920476	19960524
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 11506436	T2	19990608	JP 1996-535899	19960524
PRAI	US 1995-450646	A	19950525		
	US 1995-455768	A	19950531		
	US 1996-647132	A	19960509		
	WO 1996-US7646	W	19960524		
OS	MARPAT 126:89360				
GI					



AB Title compds. [(addnl.-substituted) I; R<sub>2</sub> = Z<sub>2</sub>Z<sub>1</sub>R<sub>1</sub>; R<sub>1</sub> = N-containing heterocyclyl; R<sub>3</sub> = Z<sub>3</sub>Z<sub>R</sub>; R = CO<sub>2</sub>H, alkoxy carbonyl, SO<sub>3</sub>H, CONHNHSO<sub>2</sub>CF<sub>3</sub>, etc.; Z = bond (un)substituted alkylene; Z<sub>1</sub> = bond, (O- or N-interrupted)alkylene, CO, alkanoyl(alkyl), NHCO, etc.; Z<sub>2</sub> = bond, alkylene, phenylene, etc.; Z<sub>3</sub> = (alkylene)carbonylimino(alkyl), etc.; dashed line = optional bond] were prepared as integrin antagonists (no data). Thus, R<sub>4</sub>(CH<sub>2</sub>)<sub>3</sub>CH:NOH (R<sub>4</sub> = phthalimido) (preparation given) was chlorinated and the product cyclocondensed with CH<sub>2</sub>:CHCH<sub>2</sub>CO<sub>2</sub>CMe<sub>3</sub> to give, after deprotection, tert-Bu 3-(3-aminopropyl)-2-isoxazoline-5-acetate. The latter was N-alkylated with 2-methylthio-3,4,5,6-tetrahydropyrimidine hydroiodide to give, after saponification, amidation by H<sub>2</sub>NCH<sub>2</sub>CH(NHSO<sub>2</sub>Ph)CO<sub>2</sub>Me,

compounds in spec

and saponification, title compound II.

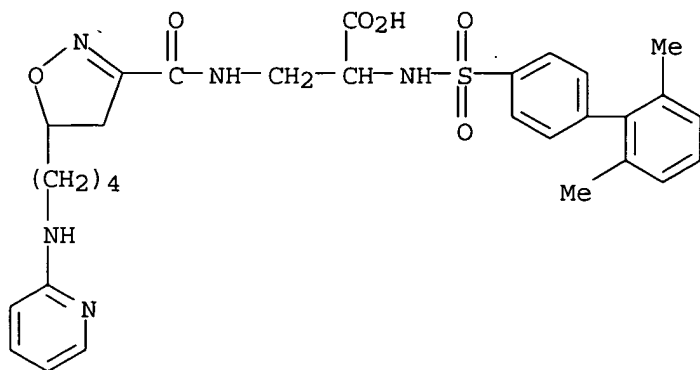
IT **185560-79-6P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of [(isoxazolinyllalkanoyl)amino]alkanoates and analogs as integrin antagonists)

RN 185560-79-6 CAPLUS

CN Alanine, 3-[[[4,5-dihydro-5-[4-(2-pyridinylamino)butyl]-3-isoxazolyl]carbonyl]amino]-N-[(2',6'-dimethyl[1,1'-biphenyl]-4-yl)sulfonyl]- (9CI) (CA INDEX NAME)



=>

=> d his

(FILE 'HOME' ENTERED AT 13:41:40 ON 17 NOV 2004)

FILE 'REGISTRY' ENTERED AT 13:41:54 ON 17 NOV 2004

L1 STRUCTURE UPLOADED  
L2 19 S L1  
L3 946 S L1 FUL  
L4 19 S L3

FILE 'CAPLUS' ENTERED AT 13:43:33 ON 17 NOV 2004

L5 88 S L3

FILE 'REGISTRY' ENTERED AT 13:46:39 ON 17 NOV 2004

L6 STRUCTURE UPLOADED  
L7 34 S L6  
L8 608 S L6 FUL

FILE 'CAPLUS' ENTERED AT 13:47:02 ON 17 NOV 2004

L9 57 S L8

FILE 'REGISTRY' ENTERED AT 13:52:03 ON 17 NOV 2004

L10 STRUCTURE UPLOADED  
L11 0 S L10  
L12 15 S L10 FUL

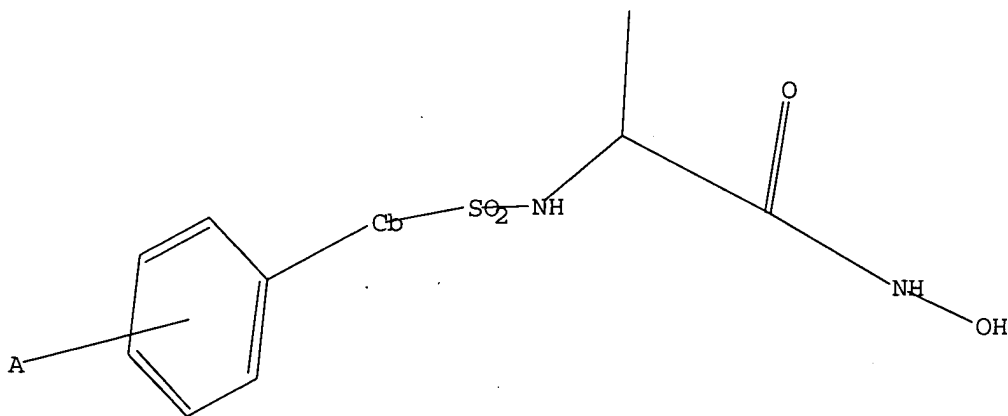
FILE 'CAPLUS' ENTERED AT 13:52:27 ON 17 NOV 2004

L13 6 S L12

=> d l10

L10 HAS NO ANSWERS

L10 STR



Structure attributes must be viewed using STN Express query preparation.

=> d bib abs hitstr 1-6

L13 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN  
AN 2003:734673 CAPLUS  
DN 139:240320  
TI Method for characterizing metabolites using hydrogen/deuterium exchange  
IN Lam, Wing Wah; Ramanathan, Ragulan  
PA Warner-Lambert Company LLC, USA  
SO Eur. Pat. Appl., 42 pp.

CODEN: EPXXDW

DT Patent  
LA English  
FAN.CNT 1

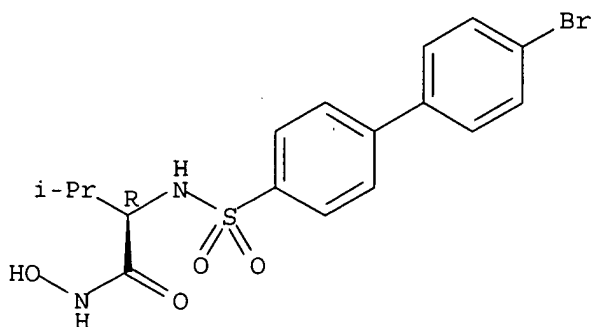
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 1345028	A1	20030917	EP 2003-4825	20030305
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	WO 2003076930	A1	20030918	WO 2003-IB883	20030303
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2003175979	A1	20030918	US 2003-387613	20030313
	JP 2004028993	A2	20040129	JP 2003-68691	20030313
PRAI	US 2002-364373P	P	20020314		

AB A system and method for performing hydrogen/deuterium (H/D) exchange in an electrospray ionization (ESI) source is described. The system includes a liquid chromatograph-mass spectrometer (LC-MS), which is equipped with an ESI source that provides for introduction of a sheath liquid. The resulting system employs deuterated solvent, such as deuterium oxide, as the sheath liquid, which allows H/D exchange expts. to be performed online. This directly provides information for determining the number and position of exchangeable hydrogens, aiding in the elucidation of the structures of drug metabolites. To demonstrate the usefulness of the invention, the hydrogen/deuterium exchange in the metabolites of PD 0200126 was examined.

IT **261625-46-1**, PD 0200126  
RL: ANT (Analyte); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study)  
(method for characterizing drug metabolites using hydrogen/deuterium exchange and liquid chromatograph-mass spectrometer with electrospray ionization source and deuterated sheath liquid applied to metabolism of PD 0200126)

RN 261625-46-1 CAPLUS  
CN Butanamide, 2-[[[4'-bromo[1,1'-biphenyl]-4-yl)sulfonyl]amino]-N-hydroxy-3-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN

AN 2002:249562 CAPLUS

DN 137:210343

TI In electrospray ionization source hydrogen/deuterium exchange LC-MS and LC-MS/MS for characterization of metabolites

AU Lam, Wing; Ramanathan, Ragu

CS Department of Pharmacokinetics, Dynamics, and Metabolism, Pfizer Global Research and Development, Ann Arbor, MI, USA

SO Journal of the American Society for Mass Spectrometry (2002), 13(4), 345-353

CODEN: JAMSEF; ISSN: 1044-0305

PB Elsevier Science Inc.

DT Journal

LA English

AB A new method is described for performing hydrogen/deuterium (H/D) exchange in an electrospray ionization (ESI) source. The use of liquid chromatog. (LC)-mass spectrometer equipped with an ESI source and deuterium oxide (D2O) as the sheath liquid allows H/D exchange expts. to be performed online. This directly provides information for determining the number and position

of exchangeable hydrogens, aiding in the elucidation of the structures of drug metabolites. To demonstrate the utility of this method, LC-mass spectrometry (MS) and LC-MS/MS expts. were performed using either H2O or D2O as sheath liquid on a matrix metalloprotease (MMP) inhibitor (PD 0200126) and its metabolites. Examination of the mass shift of the deuterated mol. from that of the protonated mol. allowed the number of exchangeable protons to be determined. Interpretation of the product-ion-spectra helped to determine the location of the exchanged protons and assisted in the assignment of the site(s) of modification for each metabolite.

IT 261625-46-1, PD 0200126

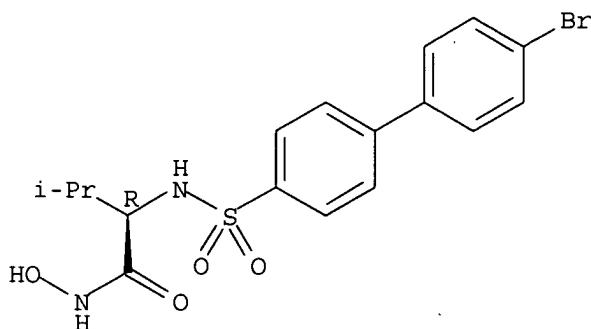
RL: ANT (Analyte); PKT (Pharmacokinetics); ANST (Analytical study); BIOL (Biological study)

(in electrospray ionization source hydrogen/deuterium exchange LC-MS and LC-MS/MS for characterization of metabolites)

RN 261625-46-1 CAPLUS

CN Butanamide, 2-[[[4'-bromo[1,1'-biphenyl]-4-yl)sulfonyl]amino]-N-hydroxy-3-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN

AN 2001:611767 CAPLUS

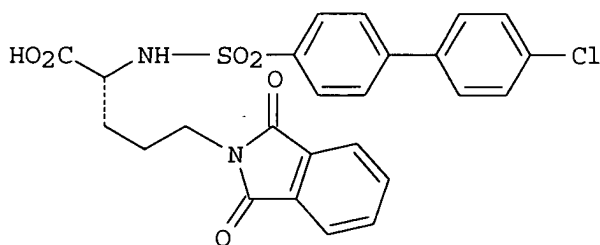
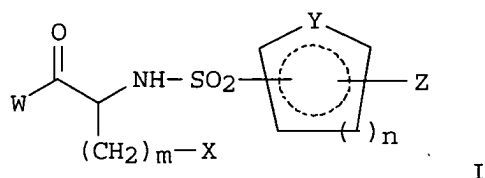
DN 135:180946

TI Preparation of sulfonylamino acid derivatives and sulfonylamino hydroxamic acid derivatives as inhibitors of matrix metalloproteinases

IN Kukkola, Paivi Jaana; Robinson, Leslie Anne; Nakajima, Motowo; Sakaki,

Junichi  
 PA Novartis A.-G., Switz.  
 SO U.S., 38 pp.  
 CODEN: USXXAM  
 DT Patent  
 LA English  
 FAN. CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6277987	B1	20010821	US 1999-243854	19990203
PRAI	US 1998-135514P	P	19980204		
OS	MARPAT 135:180946				
GI					



AB Title compds. I [W = OH, NHOH; X = heterocycle with N such that X is attached to (CH<sub>2</sub>)<sub>m</sub> group by a ring N, CONR<sub>2</sub>R<sub>3</sub>, NR<sub>1</sub>COR<sub>2</sub>, NR<sub>1</sub>SO<sub>2</sub>R<sub>2</sub>, NR<sub>1</sub>CONR<sub>2</sub>R<sub>3</sub>, NR<sub>1</sub>CO<sub>2</sub>R<sub>4</sub>, heteroarylthio, alkylthio, arylalkylthio, heteroarylalkylthio, heterocycloalkylalkylthio, heterocycloalkylthio, arylthio; Y = C, N, O, S provided when Y = C, n = 2; Z = alkyl, aryl, alkoxy, aryloxy, aralkoxyaryl, aralkoxyheteroaryl, heteroaryl, heterocycloalkyl, heteroaryloxy, CONR<sub>2</sub>N<sub>3</sub>, NR<sub>1</sub>COR<sub>2</sub>, NR<sub>1</sub>CONR<sub>2</sub>R<sub>3</sub>, OCONR<sub>2</sub>R<sub>3</sub>, NR<sub>1</sub>CO<sub>2</sub>R<sub>4</sub>, SO<sub>2</sub>R<sub>2</sub>; R<sub>1</sub> = H, alkyl, heterocycloalkylalkyl, aralkyl, heteroarylalkyl; R<sub>2</sub>, R<sub>3</sub> = R<sub>1</sub>, aryl, heteroaryl; R<sub>2</sub>R<sub>3</sub> = 5- to 7-membered ring which may optionally contain O, N and S; R<sub>4</sub> = alkyl, heterocycloalkylalkyl, aralkyl, aryl, heteroaryl; m = 1-6; n = 1, 2] were prepared. For example, the synthesis of sulfonylamino acid II involved the following steps: coupling of (R)-BocNHCH(CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>I)CO<sub>2</sub>CMe<sub>3</sub> (prepared in four steps from D-glutamic acid) with phthalimide, removal of the Boc group, coupling with 4'-chlorobiphenyl-4-sulfonyl chloride, and finally, removal of the tert-Bu ester. II inhibited stromelysin and collagenase-3 with IC<sub>50</sub> = 130 and 4 nM, resp.

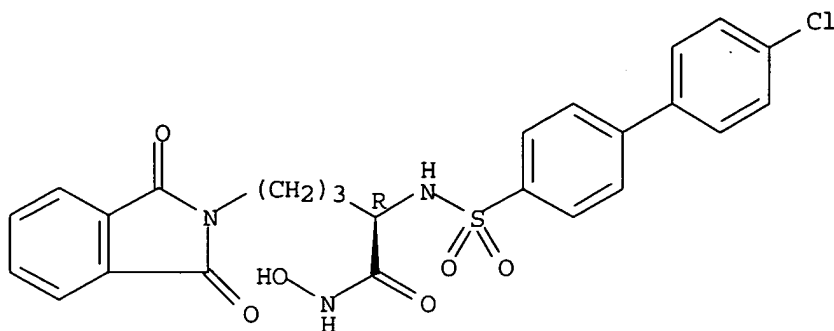
IT 240135-19-7P 240135-35-7P 240135-36-8P  
 240135-47-1P 240135-50-6P 240135-51-7P  
 240135-55-1P 240135-58-4P 240135-62-0P  
 355021-36-2P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (preparation of sulfonylamino acids and sulfonylamino hydroxamic acids as inhibitors of matrix metalloproteinases)

RN 240135-19-7 CAPLUS  
 CN 2H-Isoindole-2-pentanamide, α-[[[4'-chloro[1,1'-biphenyl]-4-

yl)sulfonyl]amino]-1,3-dihydro-N-hydroxy-1,3-dioxo-, ( $\alpha$ R)- (9CI)  
(CA INDEX NAME)

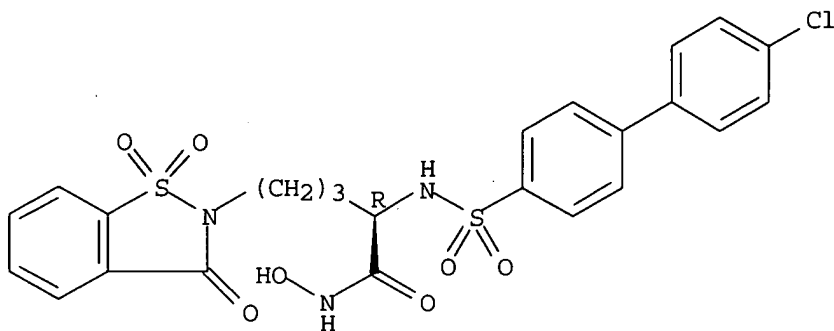
Absolute stereochemistry.



RN 240135-35-7 CAPLUS

CN 1,2-Benzisothiazole-2(3H)-pentanamide,  $\alpha$ -[[[4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]amino]-N-hydroxy-3-oxo-, 1,1-dioxide, ( $\alpha$ R)- (9CI) (CA INDEX NAME)

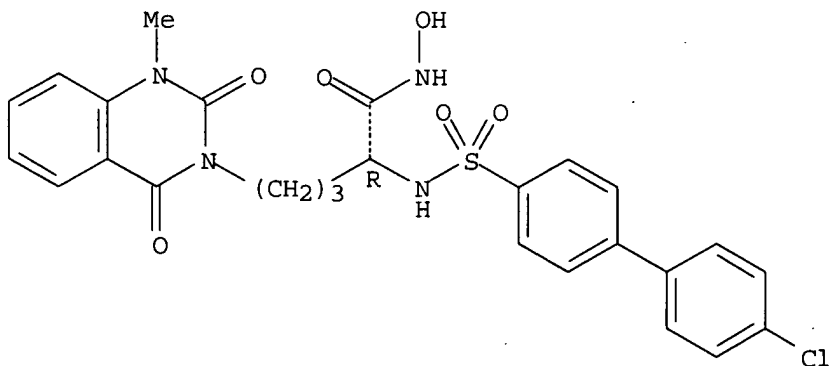
Absolute stereochemistry.



RN 240135-36-8 CAPLUS

CN 3(2H)-Quinazolinepentanamide,  $\alpha$ -[[[4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]amino]-1,4-dihydro-N-hydroxy-1-methyl-2,4-dioxo-, ( $\alpha$ R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

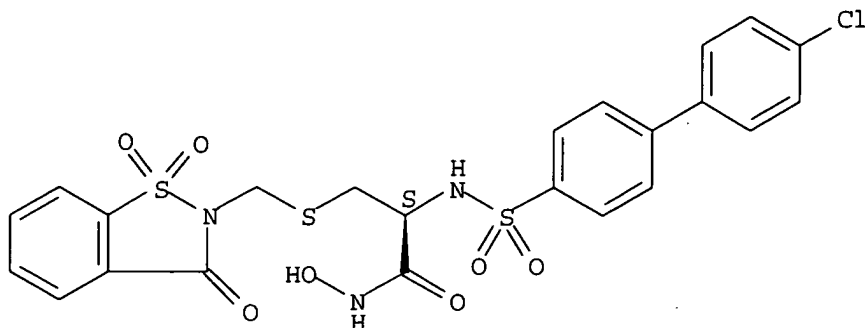


RN 240135-47-1 CAPLUS



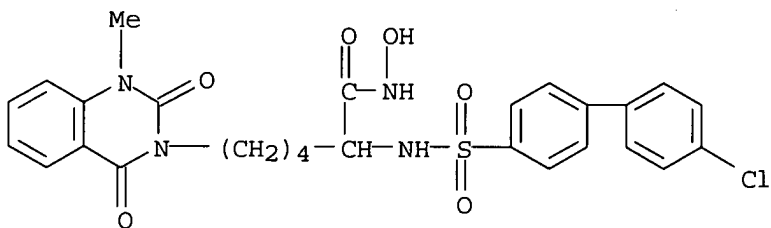
CN Propanamide, 2-[[[4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]amino]-3-[[[(1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl)methyl]thio]-N-hydroxy-, (2S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



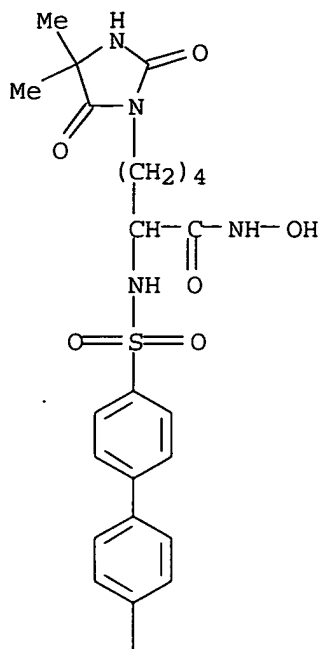
RN 240135-50-6 CAPLUS

CN 3(2H)-Quinazolinehexanamide,  $\alpha$ -[[[4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]amino]-1,4-dihydro-N-hydroxy-1-methyl-2,4-dioxo- (9CI) (CA INDEX NAME)



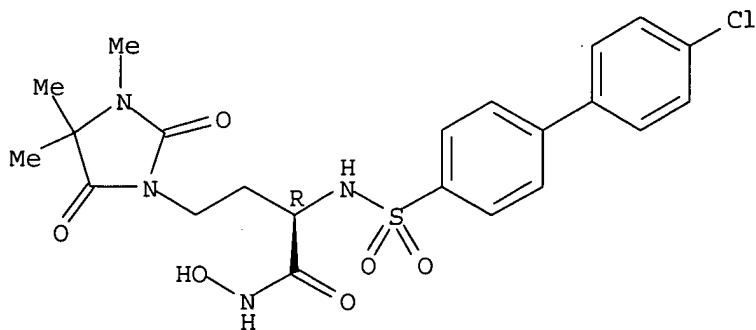
RN 240135-51-7 CAPLUS

CN 1-Imidazolidinehexanamide,  $\alpha$ -[[[4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]amino]-N-hydroxy-4,4-dimethyl-2,5-dioxo- (9CI) (CA INDEX NAME)

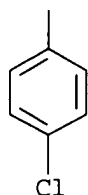
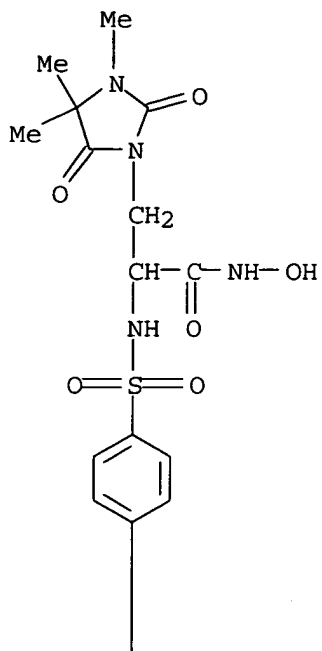


RN 240135-55-1 CAPLUS  
 CN 1-Imidazolidinebutanamide,  $\alpha$ -[[[(4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]amino]-N-hydroxy-3,4,4-trimethyl-2,5-dioxo-, ( $\alpha$ R)- (9CI)  
 (CA INDEX NAME)

Absolute stereochemistry.

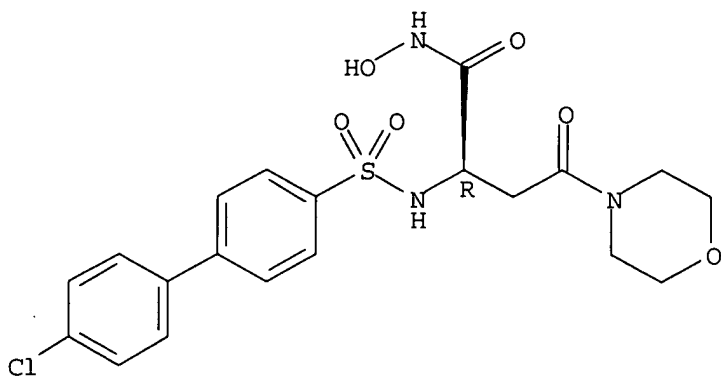


RN 240135-58-4 CAPLUS  
 CN 1-Imidazolidinepropanamide,  $\alpha$ -[[[(4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]amino]-N-hydroxy-3,4,4-trimethyl-2,5-dioxo- (9CI) (CA INDEX NAME)



RN 240135-62-0 CAPLUS  
 CN 4-Morpholinebutanamide,  $\alpha$ -[[[4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]amino]-N-hydroxy- $\gamma$ -oxo-, ( $\alpha$ R) - (9CI) (CA INDEX NAME)

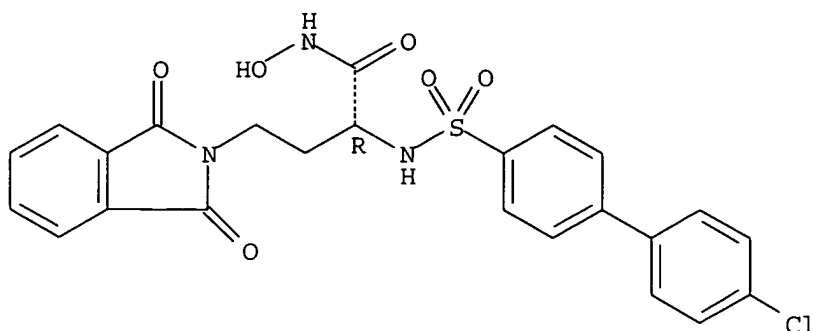
Absolute stereochemistry.



RN 355021-36-2 CAPLUS  
 CN 2H-Isoindole-2-butanamide,  $\alpha$ -[[[4'-chloro[1,1'-biphenyl]-4-

yl)sulfonyl]amino]-1,3-dihydro-N-hydroxy-1,3-dioxo-, ( $\alpha$ R) - (9CI)  
(CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN

AN 2001:137181 CAPLUS

DN 134:178144

TI Preparation of sulfonamido- and sulfinamido-containing carboxylic and hydroxamic acids derived from  $\alpha,\alpha'$ -disubstituted amino acids useful as matrix metalloproteinase inhibitors.

IN Conrad, Christopher Alan; O'Brien, Patrick Michael; Ortwine, Daniel Fred; Picard, Joseph Armand; Sliskovic, Drago Robert

PA Warner-Lambert Company, USA

SO PCT Int. Appl., 70 pp.

CODEN: PIXXD2

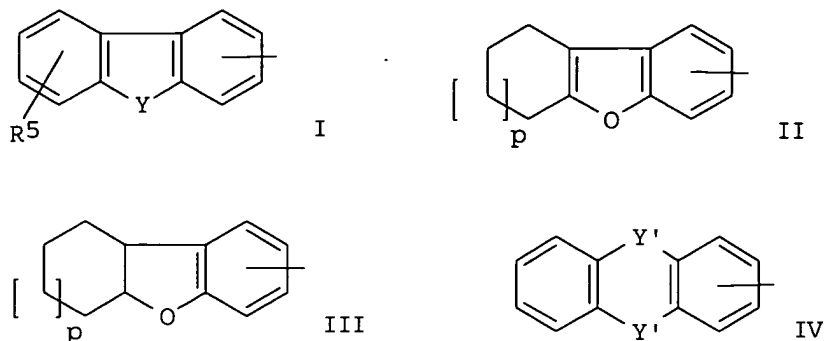
DT Patent

LA English

FAN.CNT 1

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PI	WO 2001012592	A2	20010222	WO 2000-US21884	20000810
	WO 2001012592	A3	20010705		
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	RW:				
	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
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	BR 2000013390	A	20020430	BR 2000-13390	20000810
	EP 1210326	A2	20020605	EP 2000-955435	20000810
	EP 1210326	B1	20040225		
	R:				
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	TR 200202165	T2	20021121	TR 2002-200202165	20000810
	TR 200202211	T2	20021121	TR 2002-200202211	20000810
	JP 2003507362	T2	20030225	JP 2001-516893	20000810
	AT 260251	E	20040315	AT 2000-955435	20000810
	PT 1210326	T	20040730	PT 2000-955435	20000810
	US 6677355	B1	20040113	US 2002-49544	20020213
PRAI	US 1999-149660P	P	19990818		

OS  
 GI



AB R1S(O)dNR2CR3R4C(O)X (I; e.g. 1-(dibenzofuran-3-sulfonylamino)cyclohexanecarboxylic acid) or a pharmaceutically acceptable salt thereof are useful for inhibiting matrix metalloproteinase enzymes in animals, and as such, prevent and treat diseases resulting from the breakdown of connective tissues. In I, X = OH, NHOH; R1 = II, III, IV, 4-ArMpiperidino, 4-Arppiperazino, 4-(N-(4-R5phenyl)-4-piperidinyl)phenyl, 4-(4-(4-R5phenyl)piperazino)phenyl, V; Y = O, S, -S(O)d (d = 1, 2), CH2, C(O), and NRq (Rq = H, C1-6 alkyl, or C1-6 alkylphenyl); each Y' = O, S, SO2, CH2, C(O), and NH; M = O, S, CH2; R5 = H, C1-10 alkyl, CF3, CONH2, halo, CN, COOH, C1-4 alkoxy, CHO, NO2, OH, (CH2)pOH, (CH2)pNH2, Ar, and NH2; p = 0-3; Ar = (a) phenyl; (b) Ph substituted with C1-4 alkyl, C, C1-4 alkoxy, halo, NH2, NO2, CN, COOH, CONH2, CF3, or COOR6 (R6 = C1-10 alkyl); and (c) heteroaryl; R2 = (a) H; (b) C1-4 alkyl; (c) benzyl; and (d) benzyl substituted with  $\geq 1$  C1-4 alkyl, C1-4 alkoxy, F, Cl, Br, I, NH2, NO2, CN, carboxy, and CO2R7 (R7 = H or C1-4 alkyl); and R3 and R4 are either (1) C1-20 alkyl; C3-10 cycloalkyl; phenyl; Ph substituted with C1-4 alkyl, C1-4 alkoxy, halo, NH2, NO2, CN, COOH, CO2R7, or CF3; C3-10 heterocyclic; and heteroaryl; or (2) substituents taken together to form a group of the empirical formula  $-(CH_2)_sZ_g-$ , wherein said substituents form a ring including the carbon atom adjacent the carbonyl group in I, and wherein s = 2-10; g = 0-6; and each Z is located at any position of said substituents and each Z = O, S, and NR8 (R8 = H, C1-3 alkyl). Also disclosed are pharmaceutical compns. and methods of treating diseases in which matrix metalloproteinases are involved including multiple sclerosis, atherosclerotic plaque rupture, restenosis, aortic aneurysm, heart failure, periodontal disease, corneal ulceration, burns, decubital ulcers, chronic ulcers or wounds, cancer metastasis, tumor angiogenesis, osteoporosis, rheumatoid or osteoarthritis, renal disease, left ventricular dilation, or other autoimmune or inflammatory diseases dependent upon tissue invasion by leukocytes. Other diseases for which I are claimed effective are: stroke, head trauma, spinal cord injury, Alzheimer's disease, amyotrophic lateral sclerosis, cerebral amyloid angiopathy, AIDS, Parkinson's disease, Huntington's disease, prion diseases, myasthenia gravis, and Duchenne's muscular dystrophy. Results of measurement of IC50 for matrix metalloproteinase enzyme inhibition are presented for 7 examples of I. Although the methods of preparation are not claimed, 33 example preps. are included.

IT **326499-75-6P**, 2-(4'-Bromobiphenyl-4-sulfonylamino)-N-hydroxy-2-methylpropionamide

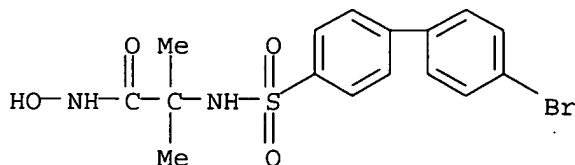
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of sulfonamido- and sulfinamido-containing carboxylic and

hydroxamic acids derived from  $\alpha,\alpha'$ -disubstituted amino acids useful as matrix metalloproteinase inhibitors)

RN 326499-75-6 CAPLUS

CN Propanamide, 2-[[[4'-bromo[1,1'-biphenyl]-4-yl)sulfonyl]amino]-N-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



L13 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN

AN 2000:3495 CAPLUS

DN 132:231496

TI Structure-activity relationships and pharmacokinetic analysis for a series of potent, systemically available biphenylsulfonamide matrix metalloproteinase inhibitors

AU O'Brien, Patrick M.; Ortwine, Daniel F.; Pavlovsky, Alexander G.; Picard, Joseph A.; Sliskovic, Drago R.; Roth, Bruce D.; Dyer, Richard D.; Johnson, Linda L.; Man, Chiu Fai; Hallak, Hussein

CS Departments of Chemistry Biochemistry and Pharmacokinetics/Drug Metabolism, Parke-Davis Pharmaceutical Research Division of Warner Lambert Company, Ann Arbor, MI, 48105, USA

SO Journal of Medicinal Chemistry (2000), 43(2), 156-166

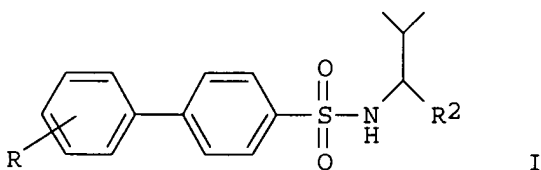
CODEN: JMCMAR; ISSN: 0022-2623

PB American Chemical Society

DT Journal

LA English

GI



AB A series of biphenylsulfonamide derivs. of (S)-2-(biphenyl-4-sulfonylamino)-3-methylbutyric acid (I) were prepared and evaluated for their ability to inhibit matrix metalloproteinases (MMPs). For this series of compds., our objective was to systematically replace substituents appended to the biphenyl and  $\alpha$ -position of 5 with structurally diverse functionalities to assess the effects these changes have on biol. and pharmacokinetic activity. The ensuing structure-activity relationship (SAR) studies showed that biphenylsulfonamides substituted with bromine in the 4'-position (II) significantly improved in vitro activity and exhibited superior pharmacokinetics ( $C_{max}$ ,  $t_{1/2}$ , AUCs), relative to compound I. Varying the lipophilicity of the  $\alpha$ -position by replacing the iso-Pr group of II with a variety of substituents, in general, maintained potency vs. MMP-2, -3, and -13 but decreased the oral systemic availability. Subsequent evaluation of its enantiomer, (R-isomer) of II, showed that both compds. were equally effective MMP inhibitors. In contrast, the corresponding hydroxamic acid enantiomeric pair, (III) and (R-isomer) of III,

stereoselectivity inhibited MMPs. For the first time in this series, (R-isomer) of III provided nanomolar potency against MMP-1, -7, and -9 (IC50's = 110, 140, and 18 nM, resp.), whereas III was less potent against these MMPs (IC50's = 24, 78, and 84  $\mu$ M, resp.). However, unlike II, compound 16a' afforded very low plasma concns. following a single 5 mg/kg oral dose in rat. Subsequent X-ray crystal structures of the catalytic domain of stromelysin (MMP-3CD) complexed with inhibitors from closely related series established the differences in the binding mode of carboxylic acid-based inhibitors II and (R-isomer) of II relative to the corresponding hydroxamic acids III and (R-isomer) of III.

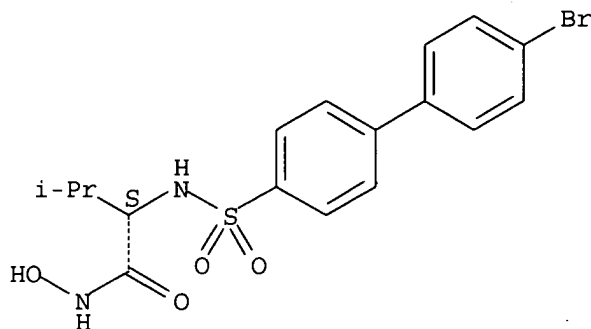
IT 261625-44-9P 261625-46-1P 261625-48-3P  
261625-50-7P

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)  
(biphenylsulfonamide MMP inhibitors SAR and pharmacokinetic anal.)

RN 261625-44-9 CAPLUS

CN Butanamide, 2-[[[4'-bromo[1,1'-biphenyl]-4-yl)sulfonyl]amino]-N-hydroxy-3-methyl-, (2S)- (9CI) (CA INDEX NAME)

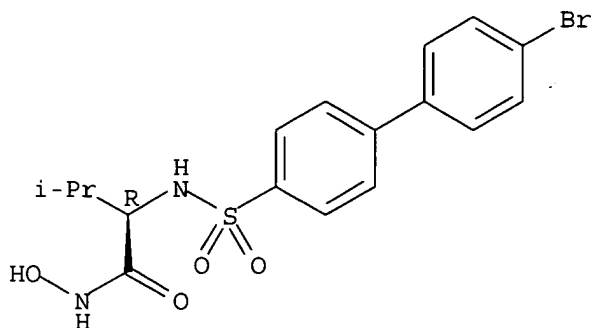
Absolute stereochemistry.



RN 261625-46-1 CAPLUS

CN Butanamide, 2-[[[4'-bromo[1,1'-biphenyl]-4-yl)sulfonyl]amino]-N-hydroxy-3-methyl-, (2R)- (9CI) (CA INDEX NAME)

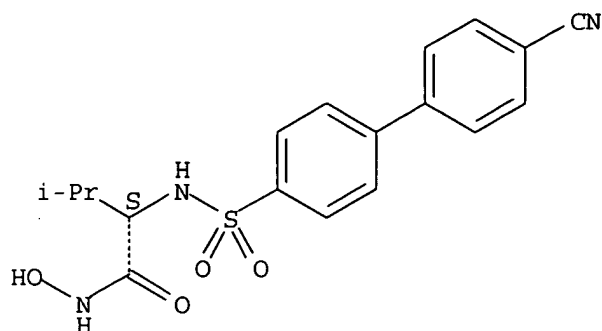
Absolute stereochemistry.



RN 261625-48-3 CAPLUS

CN Butanamide, 2-[[[4'-cyano[1,1'-biphenyl]-4-yl)sulfonyl]amino]-N-hydroxy-3-methyl-, (2S)- (9CI) (CA INDEX NAME)

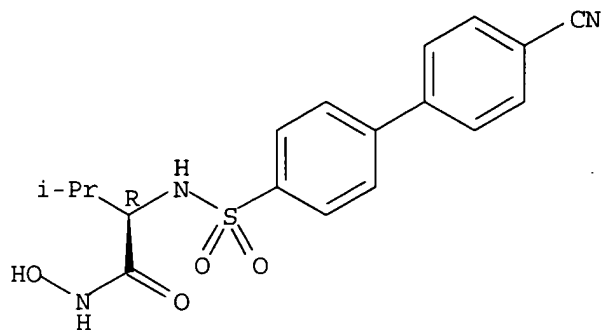
Absolute stereochemistry.



RN 261625-50-7 CAPLUS

CN Butanamide, 2-[[4'-(4-cyano[1,1'-biphenyl]-4-yl)sulfonyl]amino]-N-hydroxy-3-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN

AN 1999:549253 CAPLUS

DN 131:184961

TI Preparation of 1,2-benzisothiazole, quinazoline, imidazole, and morpholine sulfonylamino derivatives as matrix-degrading metalloproteinase inhibitors

IN Kukkola, Paivi Jaana; Robinson, Leslie Anne; Sakaki, Junichi; Nakajima, Motowo

PA Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.

SO PCT Int. Appl., 87 pp.

CODEN: PIXXD2

DT Patent

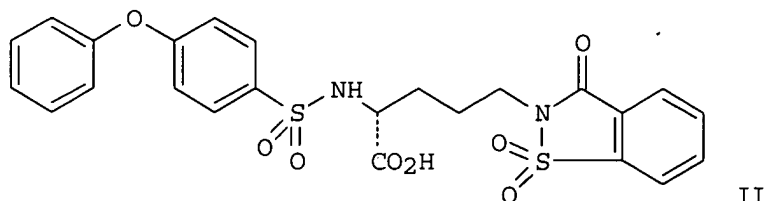
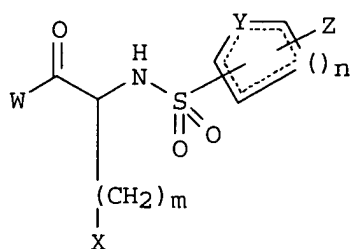
LA English

FAN.CNT 1

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CA 2318145	AA	19990826	CA 1999-2318145	19990202
AU 9929235	A1	19990906	AU 1999-29235	19990202
AU 747911	B2	20020530		
EP 1053226	A1	20001122	EP 1999-910174	19990202
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BR 9909322	A	20001205	BR 1999-9322	19990202
TR 200002224	T2	20001221	TR 2000-200002224	19990202
JP 2002503720	T2	20020205	JP 2000-532395	19990202
NZ 505968	A	20030328	NZ 1999-505968	19990202
RU 2208609	C2	20030720	RU 2000-123166	19990202
NO 2000003565	A	20001003	NO 2000-3565	20000711
US 6410580	B1	20020625	US 2000-601462	20000802
PRAI US 1998-18819	A	19980204		
WO 1999-EP646	W	19990202		
OS MARPAT 131:184961				
GI				



AB 1,2-Benzisothiazole, quinazoline, imidazole, and morpholine sulfonylamino derivs. (I) [wherein W = OH or NHOH; X = (un)substituted heterocycle, NR1SO2R2, heterocyclalkylthio, CONR2R3, or NR1COR2; Y = C, N, O, or S, provided that when Y = C, n = 2; Z = (un)substituted alkyl, (hetero)aryl, alkoxy, (hetero)aryloxy, or heterocyclalkyl, CONR2R3, NR1COR2, NR1CONR2R3, OCONR2R3, NR1COOR4, or SO2R2Z; R1, R2, R3, R4 = independently H, (aryl)alkyl, heterocyclalkyl, heteroarylalkyl, or R2 and R3 taken together with the N to which they are attached form a 5- to 7-membered (un)substituted ring; m = 1-6; n = 1 or 2] were prepared as matrix-degrading metalloproteinase inhibitors for treatment of inflammatory conditions, osteoarthritis, rheumatoid arthritis, and tumors (no data). Thus, (2R)-(BOC-amino)-5-iodopentanoic acid t-Bu ester was added to a solution of saccharin in 18-crown-6 and DMF followed by addition of DMF to yield (2R)-t-butoxycarbonylamino-5-(1,1,3-trioxo-2,3-dihydrobenzothiazol-2-yl)pentanoic acid t-Bu ester. The amide was deprotected by treatment with TFA in methylene chloride to give the amine. 4-Phenoxybenzenesulfonyl chloride (preparation given) was added to (2R)-amino-5-(1,1,3-trioxo-2,3-dihydrobenzothiazol-2-yl)pentanoic acid t-Bu ester in dioxane and TEA to form the sulfonamide followed by deesterification to yield (2R)-(4-phenoxybenzenesulfonylamino)-5-(1,1,3-trioxo-2,3-dihydrobenzothiazol-2-yl)pentanoic acid (II).

IT 240135-19-7P 240135-35-7P 240135-36-8P  
 240135-47-1P 240135-50-6P 240135-51-7P  
 240135-55-1P 240135-58-4P 240135-62-0P

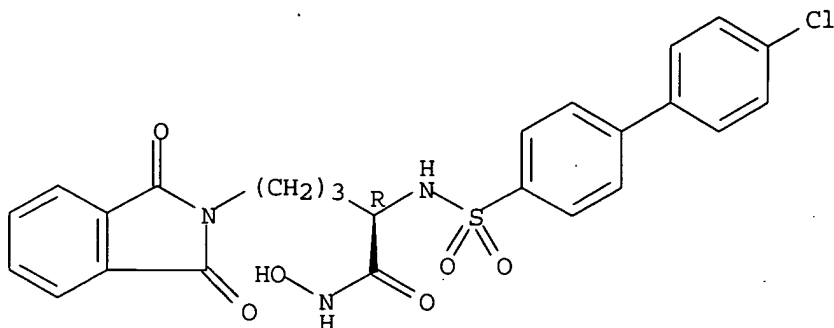
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of 1,2-benzisothiazole, quinazoline, imidazole, and morpholine sulfonylamino derivs. as matrix-degrading metalloproteinase inhibitors)

RN 240135-19-7 CAPLUS

CN 2H-Isoindole-2-pentanamide,  $\alpha$ -[[[4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]amino]-1,3-dihydro-N-hydroxy-1,3-dioxo-, ( $\alpha$ R)- (9CI)  
(CA INDEX NAME)

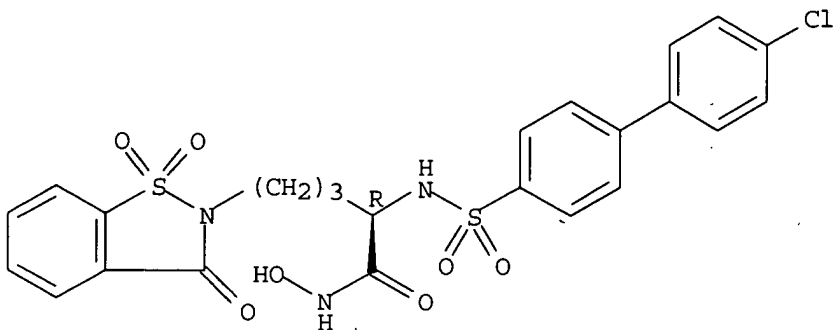
Absolute stereochemistry.



RN 240135-35-7 CAPLUS

CN 1,2-Benzisothiazole-2(3H)-pentanamide,  $\alpha$ -[[[4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]amino]-N-hydroxy-3-oxo-, 1,1-dioxide, ( $\alpha$ R)- (9CI) (CA INDEX NAME)

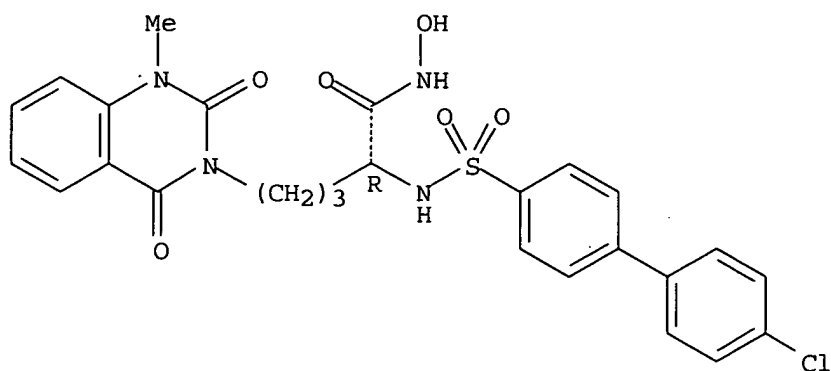
Absolute stereochemistry.



RN 240135-36-8 CAPLUS

CN 3(2H)-Quinazolinepentanamide,  $\alpha$ -[[[4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]amino]-1,4-dihydro-N-hydroxy-1-methyl-2,4-dioxo-, ( $\alpha$ R)- (9CI) (CA INDEX NAME)

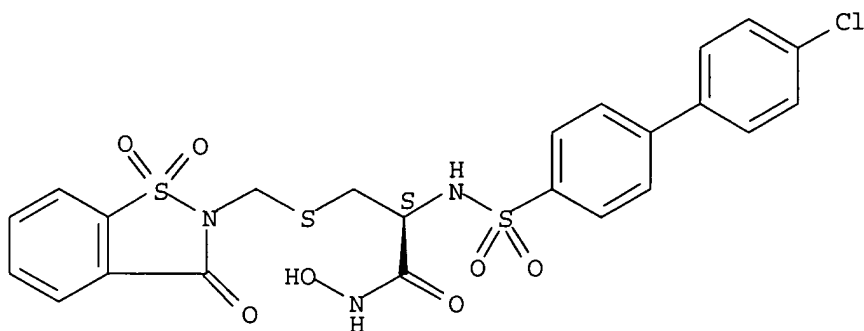
Absolute stereochemistry.



RN 240135-47-1 CAPLUS

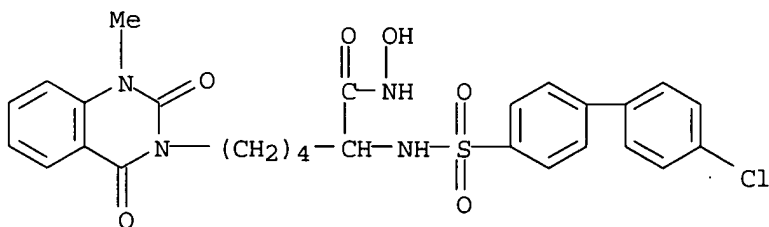
CN Propanamide, 2-[[[(4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]amino]-3-[[[(1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl)methyl]thio]-N-hydroxy-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



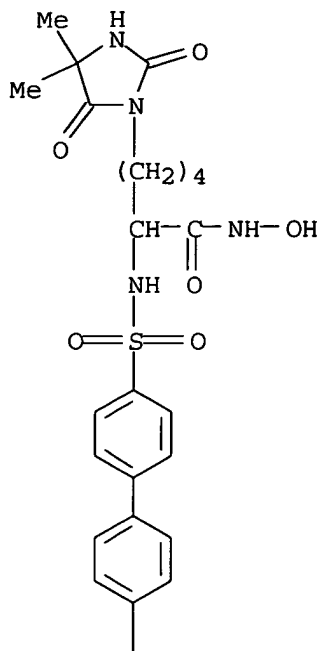
RN 240135-50-6 CAPLUS

CN 3(2H)-Quinazolinehexanamide,  $\alpha$ -[[[(4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]amino]-1,4-dihydro-N-hydroxy-1-methyl-2,4-dioxo- (9CI) (CA INDEX NAME)



RN 240135-51-7 CAPLUS

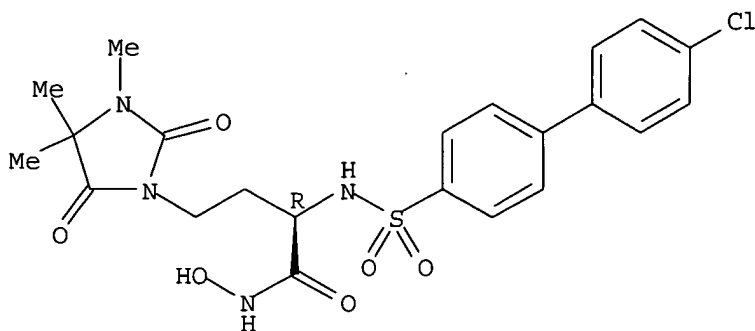
CN 1-Imidazolidinehexanamide,  $\alpha$ -[[[(4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]amino]-N-hydroxy-4,4-dimethyl-2,5-dioxo- (9CI) (CA INDEX NAME)



RN 240135-55-1 CAPLUS

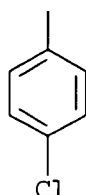
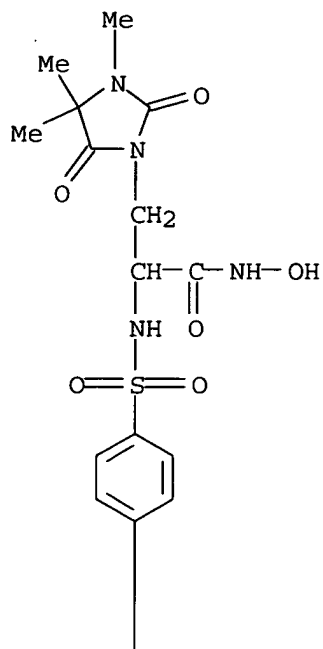
CN 1-Imidazolidinebutanamide,  $\alpha$ -[[[4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]amino]-N-hydroxy-3,4,4-trimethyl-2,5-dioxo-, ( $\alpha$ R)- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry.



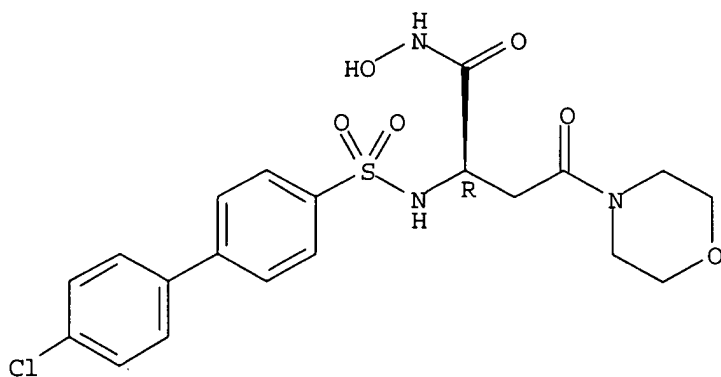
RN 240135-58-4 CAPLUS

CN 1-Imidazolidinepropanamide,  $\alpha$ -[[[4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]amino]-N-hydroxy-3,4,4-trimethyl-2,5-dioxo- (9CI) (CA INDEX NAME)



RN 240135-62-0 CAPLUS  
 CN 4-Morpholinebutanamide,  $\alpha$ -[[4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]amino]-N-hydroxy- $\gamma$ -oxo-, ( $\alpha$ R) - (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT